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P. Miller · S. M. Lawrie · A. Hodges · R. Clafferty · R. Cosway · E. C. Johnstone

Genetic liability, illicit drug use, life stress and psychotic symptoms: preliminary findings from the Edinburgh study of people at high risk for schizophrenia

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Abstract *Background:* Studies of groups at high risk of developing schizophrenia have tended to be based on subjects recruited to the study in their infancy. This paper reports on subjects at genetic high risk for schizophrenia assessed as young adults, close to the age when most onsets of schizophrenia occur. *Methods:* One hundred and fifty-five young people at elevated risk for the development of schizophrenia and 36 controls not at increased risk were assessed on entry to the Edinburgh High Risk Study. The measures included current psychotic symptoms, past and present cannabis and other drug use, lifetime life events and two aspects of genetic liability to schizophrenia. *Results:* Cannabis and other illicit drug use were significantly associated with symptoms in both groups. The same held true for the more upsetting life events experienced, but not for less upsetting ones. Within the high-risk group, there was no relationship between symptoms and a measure of genetic loading, but there was some slight evidence of a higher risk of symptoms when affected relatives were on the father's rather than the mother's side of the family. *Conclusions:* Cannabis use, use of other illicit substances and upsetting life events may all lead to psychotic symptoms in vulnerable young people.

Introduction

The Edinburgh High Risk Study [1–3] seeks to assess young people at enhanced risk of schizophrenia for genetic reasons at a time before illness develops and to monitor their progress through the critical years during which most onsets of schizophrenia occur. It differs from the generality of such high risk studies in that the subjects are recruited, not as infants, but as young adults, when the matter of whether or not they are likely to develop schizophrenia is likely to be resolved within 5–10 years. None of the subjects was clinically ill on entry to the study, but several of them did manifest one or more psychotic symptoms (e. g. isolated hallucinations). In the current paper we present some of the data on variables that might be either causes or triggers for psychotic symptoms; namely, two aspects of genetic liability, subjects' past alcohol and illicit drug use and their life events prior to entry to the study. For most of these variables, a comparison group of subjects without symptoms or illness is available, although, unfortunately, a further comparison group of first-episode schizophrenic patients could not be used because data on life events were unobtainable on nearly half of them. The expectations are that adverse levels of all the variables listed will be associated with symptoms. In addition, following Norman and Malla [4], we tested the hypothesis of an interaction between life stress and genetic liability, i. e. that symptoms would be associated with high levels of genetic risk coupled with low levels of stress or low levels of risk coupled with high levels of stress.

It has long been known that there is a familial component to schizophrenic illness. Approximately 13 % of people with a parent who suffered from schizophrenia develop the illness, as against only about 1 % in the general population [5]. Furthermore, the risk of schizotypy, a condition featuring odd behaviour and some psychotic or near psychotic symptoms is high in this group [6, 7]. In the current study we explore the relationships between a new quantitative measure of the genetic loading in our high-risk subjects and their tendency to develop psychotic symptoms. Another aspect examined is the possibility of genomic imprinting, i. e. that it matters from which parent the faulty genes are derived. This possibility does not seem to have been extensively investigated, and there appear to have been no studies as yet bearing on the question of lifetime risk of developing schizophrenia from maternal as against paternal transmission. However, three studies [8–10] all found no imprinting ef-

P. Miller (✉) · S. M. Lawrie · A. Hodges · R. Clafferty · R. Cosway · E. C. Johnstone
University Department of Psychiatry
Kennedy Tower
Royal Edinburgh Hospital
Morningside Park
Edinburgh EH10 5HF, UK

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fect on the age of first onset for schizophrenic patients, and two of these [8, 10] disagree as to whether maternal transmission is associated with the negative symptoms of schizophrenia. However, both studies are based on rather small numbers, particularly of paternal transmissions. Another much larger investigation [11] found no evidence of a parent of origin effect for schizophrenic illness, but there have been no studies to our knowledge of the association of modes of transmission with psychotic symptoms rather than illness.

Clearly, there is at present no simple complete and sufficient genetic explanation for schizophrenia, and several suggestions have been put forward of other factors that may be involved. One of these, which has been extensively studied, is the role of life events. This issue was initially addressed in the 1960 s [12, 13], with the finding that people with schizophrenia had experienced more life events prior to illness onset than had normal controls. The authors of one review [4] conclude that there is a relationship between stressors and schizophrenic symptoms over time. In particular, it seems that life stressors tend to cluster in the period (3 weeks to 3 months) immediately preceding onset of schizophrenia. One exception to this is a more recent study carried out in India [14], which found that the main clustering occurred 3–6 months prior to onset. The authors also suggest that summation of several minor stressors may not be equivalent to a single major stressor in causing onset. Three studies [15–17] found that life stress appeared to be more potent for first rather than subsequent onsets. One investigation [18] did not find this. In the present study we divide life stressors prior to entry into the study into major, intermediate and minor stressors, and examine the relationships to psychotic symptoms.

The role of substance misuse in precipitating psychotic symptoms is well established. The use of lysergic acid diethylamide (LSD) is associated with sensory distortions and hallucinations, which generally resolve over a matter of days, although characteristically transient flashbacks may occur months after drug use has ceased [19]. The fact that amphetamines can produce a state which, although temporary, may resemble paranoid schizophrenia is very well established [20, 21]. Paranoid symptoms of a similar nature may accompany the use of cocaine, psilocybin and phencyclidine [22]. The nature of the relationship between cannabis use and psychosis has caused more controversy. Evidence that cannabis is an independent risk factor in the development of schizophrenia comes from a prospective study of Swedish conscripts who were followed up over a 15-year period [23, 24]. The relative risk of developing schizophrenia was 2.4 for cannabis users and 6.0 for heavy users of the drug when compared with non-users at conscription. However, another study [25] suggests that there may be causation in both directions. Although the view that there is a 'cannabis psychosis' with perhaps a less pessimistic outlook than schizophrenia has been put forward [26], the evidence is against this [27]. The use of cannabis among schizophrenic patients is associated with greater severity of psychotic symptoms and earlier and more frequent relapses [28, 29], and its use among healthy people with schizotypal symptomatology [30]. Both drug and alcohol misuse in schizophrenic patients are associated with a more malignant course and a worse prognosis [31, 32].

Subjects and methods

The sample

The high-risk group consisted of 155 subjects aged 16–25 (mean age 21) who, on entry to the study, had never received a diagnosis of serious psychiatric disorder, but had at least two first- or second-degree relatives who suffered from schizophrenia. This group was recruited throughout Scotland by a painstaking process involving scrutiny of psychiatric case notes followed by approaches to adolescent relatives of patients. A control group of 36 subjects with no known family history of psychotic illness, comparable to the high-risk group in age, sex and social class, was obtained partly from Edinburgh youth groups and partly from the social network of the high-risk individuals. The size of this group was chosen to match the maximum number of the high-risk subjects who might be expected to develop schizophrenia: the planned comparisons being between the high-risk subjects who become schizophrenic, people with first-episode schizophrenia from families not at risk, well controls and high-risk subjects who do not develop schizophrenia. After detailed description of the study to the subjects, written informed consent was obtained from each of them.

Measures

Symptoms

On entry to the study, all subjects received the Present State Examination (PSE) [33] and other clinical assessments. Patients were classified as having psychotic symptoms if, according to specified PSE items, listed elsewhere [2], they showed evidence of delusions, hallucinations or other behaviour commonly present in schizophrenia. In no case were these symptoms sufficiently severe to meet any established operational definition for schizophrenic or related psychotic illness, and the subjects did not regard themselves as ill.

Genetic liability

Genetic liability was approached from two points of view. Firstly, we used a quantitative scale of the intensity of genetic loading, which is described elsewhere [34]. Briefly, a multifactorial polygenic model of schizophrenia is assumed with a heritability (squared) of 0.7. The measure takes into account the genetic relationships of all individuals in each high-risk family to each other and assumes a prevalence of 0.5 for schizophrenia. The scale generated is a continuous measure running from –0.17, indicating low liability, to 0.70 indicating high liability. Within this sample it is bimodal, with one mode at 0.0 and the other at 0.38.

Secondly we used a dichotomy established by scrutiny of the family trees to determine whether the genetic liability was present in the mother's or the father's side of the family.

Alcohol and illicit drug use

Data concerning past and present use of alcohol, cannabis and illicit drugs other than cannabis were established by face-to-face interviews with the subjects.

Life events

The 61-item Schedule of Recent Experiences [35] was administered on entry to the study. Subjects recorded whether each item had ever happened to them in their lifetime and, if so, when. Using established

norms, the scale was divided into the most upsetting 20 events, to be termed 'major stressors', the next 20, termed 'intermediate stressors' and the least upsetting 21, termed 'minor stressors'.

Analyses

Data analyses were all carried out by predicting symptom status at induction to the study using logistic regression. Except for the genetic measures, where the control group was omitted, these analyses involved assessing the improvement to the model on entering first the group variable (i. e. high-risk vs control), and then one of the variables under study, e. g. cannabis use.

Results

Table 1 shows the findings on the two genetic measures included. Within the high-risk group, there was no tendency for subjects with higher genetic liability to be more prone to develop psychotic symptoms. However, subjects whose high risk derived from the father's side of the family were significantly more likely to show symptoms than other high-risk subjects.

Thirty-nine high-risk subjects had symptoms, compared to only four controls. When the group variable (high-risk/control) is entered into a logistic regression equation to predict symptoms, this difference is just significant using the improvement in model fit as the criterion (change in –2log likelihood=3.89 *df* 1, *P*=0.049). Table 2 sets out the findings when other predictor variables are entered after the group variable.

Those who used cannabis or other illicit drugs, whether currently or in the past, were significantly more likely to have symptoms. Generally, the more frequently the drugs were used, the more likely were symptoms to be observed. Lifetime experience of major stressors was also a highly significant predictor of symptoms. However, there were no significant findings for past or present alcohol use (improvement χ^2 values for past and current levels of alcohol use per week were respectively 0.80, *df*=2, and 0.01, *df*=2, after entering group member-

Table 1 Genetic liability and psychotic symptoms within the high-risk group

	No symptoms	Symptoms	Significance in predicting symptoms+
Genetic liability[a]: median (*N*, 95 % CI)	0.24 (116, 0.17–0.36)	0.15 (39, 0.05–0.38)	Mann-Whitney U *Z*=0.70 NS
Maternal or paternal gene transmission *N* (%)			
Maternal	80 (80.8 %)	19 (19.2 %)	
Paternal	34 (64.2 %)	19 (35.8 %)	Fisher exact probability=0.031

[a] Continuous but bimodal measure (see text)

Table 2 The effects of use of cannabis, other illicit drugs and major stressors on psychotic symptoms

	Controls with no symptoms *N* (%)	Controls with symptoms *N* (%)	High-risk with no symptoms *N* (%)	High-risk with symptoms *N* (%)	Odds ratios[a] (95 % CI)	Improvement χ^2 (*df*, *P*)[b]
Current cannabis use						
None	27 (84.4)	2 (50.0)	83 (72.8)	22 (56.4)		
Occasional	5 (15.6)	0 (0.0)	25 (21.9)	9 (23.1)	1.3 (0.5–3.1)	13.0 (2, < 0.01)
Frequent	0 (0.0)	2 (50.0)	6 (5.3)	8 (20.5)	7.4 (2.4–22.6)	
Past cannabis use						
None	13 (40.6)	2 (50.0)	53 (46.9)	13 (33.3)		
Occasional	19 (59.4)	1 (25.0)	52 (46.0)	15 (38.5)	1.0 (0.5–2.2)	12.7 (2, < 0.01)
Frequent	0 (0.0)	1 (25.0)	8 (7.1)	11 (28.2)	6.1 (2.1–17.6)	
Current use of other drugs						
None	30 (93.8)	1 (25.0)	99 (86.8)	25 (64.1)		
Occasional	2 (6.2)	2 (50.0)	12 (10.5)	12 (30.8)	4.9 (2.1–11.6)	14.9 (2, = 0.001)
Frequent	0 (0.0)	1 (25.0)	3 (2.6)	2 (5.1)	5.0 (0.9–26.8)	
Past use of other drugs						
None	21 (65.6)	2 (50.0)	77 (67.5)	16 (41.0)		
Occasional	9 (28.1)	1 (25.0)	30 (26.3)	16 (41.0)	2.4 (2.1–5.1)	10.2 (2, < 0.01)
Frequent	2 (6.3)	1 (25.0)	7 (6.1)	7 (17.9)	4.9 (1.7–14.7)	
Major life stressors						
None	11 (36.7)	0 (0.0)	40 (37.7)	6 (17.6)		
One	6 (20.0)	1 (25.0)	27 (25.5)	5 (14.7)	1.5 (0.5–5.2)	
Two	6 (20.0)	1 (25.0)	15 (14.2)	7 (20.6)	3.4 (1.0–11.2)	12.8 (4, < 0.05)
Three	3 (10.0)	1 (25.0)	13 (12.3)	7 (20.6)	4.2 (1.3–14.2)	
Four	4 (13.3)	1 (25.0)	11 (10.4)	9 (26.5)	5.9 (1.8–19.6)	

[a] Odds ratios of having symptoms, with reference groups 'no drug usage' or 'no major life events'
[b] Change in –2log likelihood for entry of the variable after the group variable (control/high-risk)

ship) or for 'intermediate' and 'minor' stressors (improvement χ^2 values of 9.4, *df*=6 and 2.8, *df*=7 respectively).

It is noteworthy that, on those variables where significant differences were found there are no differences in the overall rates (i. e. not making the distinction symptom vs no symptom) in the control and high-risk groups. The figures are:

- *Current cannabis use:* controls 19.4 %, high-risk group 31.4 %, χ^2=2.00 NS
- *Current other drugs:* controls 13.9 %, high-risk group 19.0 %, χ^2=0.54 NS
- *Past cannabis:* controls 58.3 %, high-risk group 56.6 %, χ^2=0.04 NS
- *Past other drugs:* controls 36.1 %, high-risk group 39.2 %, χ^2=0.12 NS
- *Major stress:* median controls 1.0, median high-risk 1.0, Mann-Whitney U test: control mean rank 88.1, high-risk mean rank 87.4, Z=0.08 NS

The hypothesis that, for the high-risk group, subjects whose genetic liability was highest would develop symptoms at lower levels of life stress was tested on five different measures of stress. Firstly, total levels of stress for each subject were assessed by summing the numbers of events experienced, each event being weighted by the mean scale value assigned to it by the authors of the scale [35]. Two similar scores were derived including only major stressors and only intermediate stressors. The fourth measure was the scale score of the most upsetting event experienced in the past 2 years, and the fifth, the scale score of the most upsetting event ever experienced. Five logistic regression analyses were then run testing the interaction between genetic liability and each of the stress measures in turn in predicting symptoms. Five similar analyses were run involving maternal or paternal gene transmission and symptom status. In none of these analyses was there a significant interaction.

Discussion

This study considered psychotic symptoms on entry to the study rather than clinically diagnosed illness at a later date. This is because, so far, only ten subjects, all of them within the high-risk group, have become clinically ill. It seems plausible that, at a later stage in the study, most or all of the results will be found to apply to associations with psychiatric disorder itself. In addition, the diagnosis of schizophrenia is made on standardised but arbitrary criteria, and studying the antecedents of symptoms that make up that diagnosis is of considerable interest.

The first set of possible causes of psychotic symptoms in young people at high risk is simply genetic liability. Within the high-risk group, we found no sign of any increased tendency to develop symptoms in those at higher risk according to our main measure of genetic liability. However, if the liability stemmed from the father's side of the family, there was a slight but significant increase in the numbers of subjects with at least one psychotic symptom. Concerning the second area explored, both the use of cannabis and the use of other illicit drugs predicted symptoms, although alcohol use did not. The experience of major life stressors before entry into the study was related to the occurrence of symptoms, but there was no indication of an interaction between life stress and genetic liability.

Our failure to demonstrate a relationship between the main genetic liability measure and current psychotic symptoms is in contrast to our findings in neuropsychological and brain imaging studies of the same subjects [1, 3]. This may reflect that the analyses carried out here are within the group of subjects at high risk, and the range of variation is somewhat limited as there are no families in which both parents are affected. In addition, as the average age of the subjects was only 21, the period of risk for symptom development is by no means over.

Our finding of greater risk of psychotic symptoms from apparent paternal transmission does not seem to have been tested elsewhere in the literature, and needs to be replicated, particularly as the effect only just reached significance without correction for number of tests.

Turning to the use of cannabis and other illicit drugs, both the controls and the high-risk group show indications (Table 2) of dose-response relationships – the higher the drug usage the more likely the presence of psychotic symptoms. Unfortunately it is not possible to test whether the relationships might be stronger in the high-risk as compared to the control group, as the number of controls with symptoms is too small. It is, however, interesting that the overall rates, irrespective of symptoms, of illicit drug use for the control and high-risk groups are not significantly different. The control subjects are, of course, unlikely to be currently using cannabis in response to psychotic symptoms. This would be possible only for the two controls who actually used cannabis. For the high-risk group there is, a priori, a greater likelihood that they might use cannabis or other drugs as self-medication for symptoms. However, if this were so, one would expect the rates of use to be higher in the high-risk group than in the controls. There was, in fact, no significant difference, although it is possible that with larger numbers there might have been. Furthermore, past cannabis use was associated with present symptoms. Self-medication for psychotic symptoms is, therefore, unlikely to afford a complete explanation of the association in the high-risk subjects. We conclude that both cannabis and the use of other illicit drugs are likely to precipitate psychotic symptoms. This is in line with findings in other studies [23–25, 28, 36, 37]. This is not to say that the illicit drugs referred to here can cause psychoses in their own right; rather, they may well act as precipitants in the otherwise predisposed.

Life stressors are associated with symptoms. In this

study, it is difficult to be sure about the direction of causation, as symptom onset dates are not known and could have been before the events. However, the overall rates of events within the high-risk and control groups are similar, suggesting, as in the case of illicit drugs, that the events may be causal. It is noteworthy that the association concerns major stressors only. Thus, if life stress is a triggering factor for symptoms, then it may be that seriously upsetting events are required. Aggregation of several smaller stresses does not appear to be sufficient.

Our findings have clinical as well as aetiological implications. Physicians who are aware that some of their younger patients have a family history of schizophrenia and regularly use illicit drugs, or have been exposed to major life stress, may wish to monitor them closely and advise them to reduce their illicit drug consumption. We have, of course, not examined whether this would reduce symptoms (or avoid any possible progression to schizophrenia) but such a strategy would at least aid early detection and may even be preventative.

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References

1. Byrne M, Hodges A, Grant E, Owens DG, Johnstone EC. Neuropsychological assessment of young people at high genetic risk for developing schizophrenia compared to controls: preliminary findings of the Edinburgh High-Risk Study. Psychol Med 1999; 29: 1161–1178
2. Johnstone EC, Abukmeil SS, Byrne M, Clafferty R, Grant E, Hodges A, Lawrie SM, Owens DG. Edinburgh High-Risk Study – findings after four years: demographic, attainment and psychopathological issues. Schizophr Res 1999; 46: 1–15
3. Lawrie SM, Whalley H, Kestelman JN, Abukmeil SS, Byrne M, Hodges A, Rimmington JE, Best JJ, Owens DG, Johnstone EC. Magnetic resonance imaging of brain in people at high risk of developing schizophrenia. Lancet 1999; 353:30–33
4. Norman RM, Malla AK. Stressful life events and schizophrenia. I. A review of research. Br J Psychiatry 1993; 162: 161–166
5. Gottesman I I. Schizophrenia genesis. New York: Freeman, 1991
6. Kendler KS, McGuire M, Gruenberg AM, Walsh D. Schizotypal symptoms and signs in the Roscommon family study: their factor structure and familial relationship with schizophrenia, other affective psychoses, and psychotic and non-psychotic affective illness. Arch Gen Psychiatry 1995; 52: 296–303
7. Kremen WS, Faraone SV, Toomey R, Seidman LJ, Tsuang MT. Sex differences in reported schizotypal traits in relatives of schizophrenic probands. Schizophr Res 1998; 34: 27–37
8. Martorell VJ, Mariné J, Vilella E, Labad A. Anticipation and imprinting in Spanish families with schizophrenia. Acta Psychiatr Scand 1998; 97: 343–350
9. Asherson P, Walsh C, Williams J, Sargeant M, Taylor C, Clements A, Gill M, Owen M, McGuffin P. Imprinting and anticipation: are they relevant to genetic studies of schizophrenia? Br J Psychiatry 1994; 164: 619–624
10. Ohara K, Xu H, Mori N, Suzuki Y, Xu D, Ohara K, Wang Z. Anticipation and imprinting in schizophrenia. Biol Psychiatry 1997; 42: 760–766
11. DeLisi LE, Razi K, Stewart J, Relja M, Shields G, Smith AB, Wellman N, Larach VW, Loftus J, Vita A, Comazzi M, Crow TJ. No evidence for a parent-of-origin effect detected in the pattern of inheritance of schizophrenia. Biol Psychiatry 2000; 48: 706–709
12. Steinberg HR, Durell J. A stressful situation as a precipitant of schizophrenic symptoms: an epidemiological study. Br J Psychiatry 1968; 114: 1097–1105
13. Brown GW, Birley JLT. Crises, life changes and the onset of schizophrenia. J Health Soc Behav 1968; 9: 203–214
14. Das MK, Kulhara PL, Verma SK. Life events preceding relapse of schizophrenia. Int J Soc Psychiatry 1997; 43: 56–63
15. Lahniers C, White K. Changes in environmental life events and their relationship to psychiatric hospital admissions. J Nerv Ment Dis 1976; 163: 154–157
16. Skodol AE, Shrout PE. Use of DSM III axis IV in clinical practice: rating the severity of psychosocial stressors. Psychiatr Res 1989; 30: 201–211
17. Castine MR, Meador-Woodruff JH, Dalack GW. The role of life events in onset and recurrent episodes of schizophrenia and schizoaffective disorder. J Psychiatr Res 2000; 32: 283–288
18. Canton G, Fraccon IG. Life events and schizophrenia: a replication. Acta Psychiatr Scand 1985; 71: 211–216
19. Horowitz MJ. Flashbacks: recurrent intrusive images after the use of LSD. Am J Psychiatry 1969; 126: 565–569
20. Connell PH. Amphetamine psychosis. Maudsley Monograph 5. London: Chapman Hall, 1958
21. Griffiths JD, Cavanagh J, Oates J. Paranoid episodes induced by drugs. J Am Med Assoc 1972; 205: 39–46
22. Barondes SH. Molecules and mental illness. New York: Scientific American Library, 1999
23. Andreasson S, Allebeck P, Engstrom A, Rydberg U. Cannabis and schizophrenia: a longitudinal study of Swedish conscripts. Lancet 1987; 330: 1483–1485
24. Andreasson S, Allebeck P, Rydberg U. Schizophrenia in users and nonusers of cannabis. Acta Psychiatr Scand 1989; 79: 505–510
25. Hambrecht M, Häfner H. Substance abuse and the onset of schizophrenia. Biol Psychiatry 1996; 40: 1155–1163
26. Imade AGT, Ebie JC. A retrospective study of symptom patterns of cannabis induced psychosis. Act Psychiatr Scand 1991; 83: 134–136
27. McGuire PK, Jones P, Harvey I, Bebbington P, Toone B, Lewis S, Murray RM. Cannabis and acute psychosis. Schizophr Res 1994; 13: 161–168
28. Linszen DH, Dingemans PM, Lenior ME. Cannabis abuse and the course of recent onset schizophrenic disorders. Arch Gen Psychiatry 1994; 51: 273–279
29. Martinez-Arevalo MJ, Calcedo-Ordonez A, Varo-Prieto JR. Cannabis consumption as a prognostic factor in schizophrenia. Br J Psychiatry 1994; 164: 679–681
30. Williams JH, Wellman NA, Rawlins JNP. Cannabis correlates with schizotypy in healthy people. Addiction 1996; 91: 869–877
31. Cantwell R, Harrison G. Substance misuse in the severely mentally ill. Adv Psychiatr Treatment 1996; 2: 117–124
32. Miller PM, Johnstone EC, Lang FH, Thomson LDG. Differences between patients with schizophrenia within and without a high security psychiatric hospital. Acta Psychiatr Scand 2000; 102: 12–18
33. Wing JK, Cooper JE, Sartorius N. The measurement and classification of psychiatric symptoms. Cambridge: Cambridge University Press, 1974
34. Lawrie SM, Whalley HC, Abukmeil SS, Kestelman JN, Donnelly L, Miller P, Best JJK, Cunningham-Owens DG, Johnstone EC. Brain structure, genetic liability and psychotic symptoms in subjects at high risk of developing schizophrenia. Biol Psychiatry 2001;49: 811–823
35. Paykel ES, Prusoff BA, Uhlenhuth AH. Scaling of life events. Arch Gen Psychiatry 1971; 25: 340–347
36. McLellan AT, Woody GE, O'Brien CP. Development of psychiatric illness in drug abusers: possible role of drug preference. New Engl J Med 1979; 301: 1310–1314
37. Lawrie SM, Hutchison JK, Sweeney SR, Fernando MR, McAdam CA, Monsour MR, Campbell TJ, McLeod CM. Psychosis and substance abuse: cause, effect or coincidence? Scot Med J 1995; 40: 174–176